



STATE OF NEVADA

Department of Conservation & Natural Resources

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DIVISION OF ENVIRONMENTAL PROTECTION

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November 27, 2006

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Re. **BMI Plant Sites and Common Areas Projects, Henderson, Nevada**
NDEP Review of Human Health Toxicological Criteria, DMPT, DEPT dated November 1, 2006
Submitted by PES Environmental on behalf of Syngenta Crop Protection

Dear Sirs and Madam:

Attachment A contains the NDEP's comments on the subject document. Please incorporate these changes and submit the finalized document.

If you have any questions, do not hesitate to contact me.

Sincerely,

Brian A. Rakvica, P.E.
Supervisor, Special Projects Branch
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Attachment A

Based on discussions between NDEP and Syngenta, Syngenta evaluated the identification of appropriate toxicological surrogates for the following chemicals:

- dimethyl phosphorodithioate (DMPT) (CASRN 756-80-9) and
- diethyl phosphorodithioate (DEPT) (CASRN 298-06-6).

The document was prepared in response to this discussion and contains the following components:

- A review of the acetylcholinesterase (AChE) inhibition potential of DMPT and DEPT;
- A review of available toxicity data for DMPT and DEPT;
- Identification of proposed toxicological surrogates; and
- Identification of proposed toxicity criteria for DMPT and DEPT based on the proposed toxicological surrogates.

Our comments regarding each of the document components are provided below.

I. AChE Inhibition Potency of DMPT and DEPT

The document provides adequate documentation that AChE inhibition is not a significant or relevant toxicological endpoint for DMPT and DEPT.

II. Identification of Toxicological Surrogates for DMPT and DEPT

Based on structural similarity, physical/chemical properties, and the availability of chronic toxicity data, the aforementioned document identified the following toxicological surrogates:

Chemical Requiring Surrogate	Toxicological Surrogate
DMPT (dimethyl phosphorodithioate)	Isopropyl methyl phosphonic acid (IMPA)
DEPT (diethyl phosphorodithioate)	Diisopropyl methyl phosphonate (DIMP)

Although other candidates were not considered in the document, the selection of DIMP and IMPA as surrogates is reasonable based on structural similarity and the availability of USEPA oral reference doses for these chemicals. We concur with the selection of DIMP as the toxicological surrogate for DMPT and the selection of IMPA as a toxicological surrogate for DEPT.

Please note that the structure presented for IMPA in Table 2 (p. 13) is not consistent with the structure identified in the Merck Index (2006), which was our source for structure confirmation. The structure identified in the Merck Index is attached to this letter as Attachment B. If the NDEP's assumption is not correct this issue will require further discussion. If the NDEP's assumption is correct the finalized document should be corrected.

III. Identification of Toxicity Criteria for DMPT and DEPT

Based on structural similarity, (limited) information regarding toxicity, and information contained in USEPA's IRIS data base (USEPA, 2006) and in the ATSDR toxicological profile for DIMP (ATSDR, 1998), we concur with the use of the USEPA oral reference doses (RfDs) for DIMP and IMPA for purposes of risk characterization of DMPT and DEPT, respectively. However, we do not concur with the application of a modifying factor to the surrogate RfDs for the following reasons:

- It is generally recognized that using a toxicological surrogate approach for health risk assessment contributes to uncertainty in the risk characterization, even when specific toxicological mechanisms and/or structure-activity-relationships are understood.
- Although DMPT and DEPT are structurally similar to the proposed surrogates, the mechanism of action for DMPT and DEPT toxicity is unknown.
- USEPA's confidence in the RfDs for both DIMP and IMPA is rated "low" (USEPA, 2006) due to limitations in the primary study and toxicity database for both of these chemicals.

IV. Summary and Conclusions

Based on the structures that we confirmed for DIMP and IMPA, we concur with the identification of these chemicals as the toxicological surrogate chemicals for DMPT and DEPT, respectively. We also concur with the applicability of the RfDs for these surrogates for purposes of assessing potential upper bound health risks associated with DMPT and DEPT in environmental media at the BMI Complex and surrounding areas. However, due to the uncertainties in comparative toxicity of DMPT and DEPT and the identified surrogates, we do not concur that the use of a "modifying factor" (which would increase the acceptable daily dose by an order of magnitude) is justified or defensible. Accordingly, for purposes of health risk assessments of DMPT and DEPT prepared for the NDEP, the RfDs for the toxicological surrogates should be applied without modification. If this methodology results in unacceptable risks for DMPT and/or DEPT, alternative risk characterization methodology and/or risk management goals should be considered.

V. References Cited

Agency for Toxic Substances and Disease Registry (ATSDR), 1998. Toxicological Profile for Diisopropyl Methylphosphonate, August. www.atsdr.cdc.gov/toxprofiles/tp119.html

The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, 2006. 14th Ed. O'Neil, M.J., Heckelman, P.E., Koch, C.B., and Roman, K.J., eds., Merck & Co., Inc., Whitehouse Station, NJ., 2520p. http://themerckindex.cambridgesoft.com.laneproxy.stanford.edu/TheMerckIndex/default.asp?formgroup=basenp_form_group&dataaction=db&dbname=TheMerckIndex

USEPA 2006. Integrated Risk Information System (IRIS). Online database of USEPA toxicity criteria. www.epa.gov/iris/

Attachment B

MERCK INDEX 2006 (online)

http://themerckindex.cambridgesoft.com.laneproxy.stanford.edu/TheMerckIndex/default.asp?formgroup=basenp_form_group&dataaction=db&dbname=TheMerckIndex

- Monograph number: 04924
- Title: IMPA
- CAS Registry Number: 1832-54-8
- CAS Name: Methylphosphonic acid mono(1-methylethyl) ester
- Additional Names: iPMPA; O-isopropyl methyl phosphonic acid; neutralized sarin
- Molecular Formula: C₄H₁₁O₃P
- Molecular Weight: 138.10
- Percent Composition: C 34.79%, H 8.03%, O 34.76%, P 22.43%
- Literature References: Degradation product of the nerve gas, [sarin](#), *q.v.* Identification as hydrolysis product: F. C. G. Hoskin, *Can. J. Biochem. Physiol.* 34, 75 (1956). Prepn as silver salt: *idem*, *Can. J. Chem.* 35, 581 (1957); of ester: J. I. G. Cadogan *et al.*, *J. Chem. Soc.* 1971, 1988. Biodisposition in mice: P. J. Little *et al.*, *Toxicol. Appl. Pharmacol.* 83, 412 (1986). Biological monitoring in human urine after sarin exposure: M. Minami *et al.*, *J. Toxicol. Sci.* 23, Suppl. II, 250 (1998). Biodegradation: Y. Zhang *et al.*, *Biotechnol. Bioeng.* 64, 221 (1999). Determn in ground water by GC with flame photometric detection: G. A. Segal *et al.*, *J. Chromatogr. A* 790, 143 (1997); LC-MS rapid determn: R. W. Read, R. M. Black, *ibid.* 862, 169 (1999).
- Properties: bp0.02 88°. *n*_D25 1.4210.
- Use: Marker for the detection of sarin.
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